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(54) Title: INHIBITORS OF c-JUN N-TERMINAL KINASES (JNK)

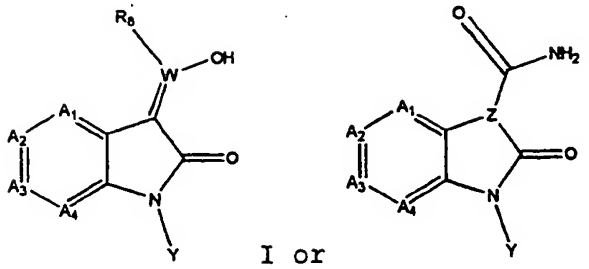
(57) Abstract

The present invention relates to compounds of formula (I) or (II), or a pharmaceutically acceptable derivative or prodrug thereof; wherein Y is selected from $-(CH_2)-Q_1$; $-(CO)-Q_1$; $-(CO)NH-Q_1$; $-(CO)-O-Q_1$; $-(SO_2)-Q_1$ or $-(SO_2)NH-Q_1$; Q_1 is a C_1–C_6 straight chain or branched alkyl or alkenyl group; a 5–7 membered aromatic or non–aromatic carbocyclic or heterocyclic ring; or a 9–14 membered bicyclic or tricyclic aromatic or non–aromatic carbocyclic or heterocyclic ring system, W is N or C; Z is CH or N, which are inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

CLAIMS

We claim:

1. A compound of the formula:



I or II,

or a pharmaceutically acceptable derivative or prodrug thereof; wherein

Y is selected from $-(CH_2)-Q_1$; $-(CO)-Q_1$; $-(CO)NH-Q_1$; $-(CO)-O-Q_1$; $-(SO_2)-Q_1$ or $-(SO_2)NH-Q_1$;

Q_1 is a C_1-C_6 straight chain or branched alkyl or alkenyl group; a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring; or a 9-14 membered bicyclic or tricyclic aromatic or non-aromatic carbocyclic or heterocyclic ring system, wherein said alkyl, alkenyl, ring or ring system is optionally substituted with one to four substituents, each of which is independently selected from NH_2, NH-R, $N(R)_2$, NO_2, OH, OR, CF_3, halo, CN, CO_2H, $C(O)-NH_2$, C(O)-NH-R, $C(O)-N(R)_2$, C(O)-R, SR, S(O)-R, $S(O)_2$-R, $S(O)_2$-NH-R or -R;

W is N or C;

wherein when W is N, R_8 is a lone pair of electrons; and

wherein when W is C, R_8 is R_7.

A_1 is N or CR^1;

A_2 is N or CR^2;

A_3 is N or CR^3;

A_4 is N or CR^4;

provided that at least one of A_1, A_2, A_3 and A_4 must not be N;

R^1 is $-NHR^5$, $-OR^5$, $-SR^5$, or $-R^5$;

R^2, R^3, and R^4 are independently selected from $-(CO)NH_2$, $-(CO)NHR$, $-(CO)N(R)_2$, $-NHR^5$, $-NHCH_2R^5$, $-OR^5$, $-SR^5$, $-R^5$, $-NH(CO)-R^6$, $-NH(CO)-NHR^6$, $-NH(CO)-NH(CO)R^6$, $-NH(CO)-OR^6$, $-NH(SO_2)-R^6$, $-NH(SO_2)-NHR^6$, $-C(O)OH$, $-C(O)OR$, $-(CO)-Q_1$, $-(CO)NH-Q_1$, $-(CO)NR-Q_1$, $-(CO)-O-Q_1$, $-(SO_2)-Q_1$ or $-(SO_2)NH-Q_1$;

R^5 and R^6 are each independently selected from H; $N(R)_2$, NHOH, NO_2, $C(O)OR$ or halo; a C_1-C_6 straight chain or branched alkyl, alkenyl or alkynyl group; a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring; or a 9-14 membered bicyclic or tricyclic aromatic or non-aromatic carbocyclic or heterocyclic ring; wherein said alkyl, alkenyl, ring or ring system is optionally substituted with one to four substituents, each of which is independently selected from NH_2, NHR, $NHC(O)OR$, $N(R)_2$, NO_2, OH, OR, CF_3, halo, CN, $Si(R)_3$, CO_2H, COOR, $CONH_2$, CONHR, $CON(R)_2$, COR, SR, $S(O)R$, $S(O)_2R$, $S(O)_2NHR$ or R;

R^7 is H; a C_1-C_6 straight chain or branched alkyl or alkenyl group; a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring; or a 9-14 membered bicyclic or tricyclic aromatic or non-aromatic carbocyclic or heterocyclic ring; wherein said alkyl, alkenyl, ring or ring system is optionally substituted with one to four substituents, each of which is independently selected from NH_2, NHR, $N(R)_2$, NO_2, OH, OR, CF_3, halo, CN, CO_2H, $CONH_2$, CONHR, $CON(R)_2$, COR, SR, $S(O)R$, $S(O)_2R$, $S(O)_2NHR$ or R;

R is a C_1-C_6 straight chain or branched alkyl or alkenyl group, a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring, or a 9-10 membered bicyclic aromatic or non-aromatic carbocyclic or

heterocyclic ring system; and

Z is CH or N.

2. The compound according to claim 1, wherein Y is $-(CH_2)-Q_1$ and Q_1 is a substituted phenyl.

3. The compound according to claim 1, wherein the compound is selected from any one of the compounds depicted in Table 1.

4. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1 to 3 effective to inhibit JNK, and a pharmaceutically acceptable carrier.

5. Use of the composition according to claim 4 for the manufacture of a medicament for treating or preventing inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with proinflammatory cytokines in a patient in need thereof.

6. The use according to claim 5, wherein said treating or preventing is for an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

7. The use according to claim 5, wherein said

treating or preventing is for an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

8. The use according to claim 5, wherein said wherein said treating or preventing is for a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

9. The use according to claim 5, wherein said wherein said treating or preventing is for a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

10. The use according to claim 5, wherein said wherein said treating or preventing is for a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

11. The use according to claim 5, wherein said wherein said treating or preventing is for ischemia/reperfusion in stroke or myocardial ischemia,

renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

12. The use according to claim 5, wherein said wherein said treating or preventing is for a condition associated with T-cell activation or pathologic immune responses.

13. The use according to claim 5, wherein said wherein said treating or preventing is for an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/40 A61K31/395 A61P43/00 C07D413/06 C07D405/06
C07D417/06 C07D401/06 C07D403/06 C07D409/04 C07D409/14
C07D405/14 C07D417/14 C07D401/14 C07F7/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
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